Reduced Hippocampal Volume in Unmedicated, Remitted Patients with Major Depression Versus Control Subjects

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Background: *Hippocampal volumes obtained from a group of medication-free, remitted subjects with recurrent major depressive disorder (MDD) were compared against corresponding measures from healthy controls.*

Methods: *Thirty-one subjects with recurrent MDD in full remission, and 57 healthy controls underwent high resolution magnetic resonance imaging (MRI) on a GE 3T scanner. Eight patients with MDD were medication-naive, and twenty-three MDD patients were off antidepressant medications for a mean of 30 months at the time of the MRI study.*

Results: *Patients showed smaller total and posterior hippocampal volume relative to controls. Anterior hippocampal volume did not differ between patients and controls.*

Conclusions: *Recurrent depression is associated with smaller hippocampal volume which is most prominent in the posterior hippocampus. Smaller hippocampal volume appears to be a trait characteristic for MDD.*

Key Words: Major depression, morphometry, hippocampal volume, high resolution MRI imaging

Reduced hippocampal volume has been reported by many, but not all, neuroimaging studies of major depressive disorder (MDD) (Campbell et al 2004). Early age-at-illness onset (MacMaster and Kusumakar 2004), number of previous episodes (MacQueen et al 2003), longer durations during which MDD went untreated (Sheline et al 2003), and early childhood abuse (Vythilingam et al 2002) appear to contribute to the hippocampal volume loss in MDD. A major limitation of these investigations pertaining to identification of the effect of MDD on hippocampal volume was that most patients were studied when being symptomatic depressed and while being on antidepressant medication at the time of their magnetic resonance imaging (MRI) study. Moreover, there is a substantive amount of variance between clinical variables, such as age, age at illness onset, length of illness, and number of episodes of the studied patients, and anatomical definitions that were used in the different studies. To overcome the limitations of previous studies, we studied a group of fully remitted, unmedicated patients with a diagnosis of recurrent MDD with early onset of illness using high resolution, 3T MRI.

Methods and Materials

We recruited 31 unmedicated (30 (34.4) months at the time of the MRI study) subjects (23 women; age 40.1 (13.1) years; age at onset of MDD 24.6 (10.3) years; 3.2 (2.1) previous episodes) with MDD in full remission (length of remission: 30.5 (33.9) months, range 3–156) and a Hamilton Depression Rating Scale Score of 1.3 (1.4) on the day of the MRI study. Patients met diagnostic criteria for recurrent MDD according to DSM-IV criteria. Some patients reported transient subsyndromal symptoms during the remission period but did not meet criteria for MDD or dysthymia or required treatment. We also recruited 57 healthy control subjects (36 women; 38.0 (10.9) years). Study participants were recruited from the community using advertisements in the local newspapers. No lifetime diagnosis of substance dependence was allowed. Subjects with a diagnosis of substance abuse within 12 months prior to the study were excluded. There was no history of trauma. Controls did not have a personal history of any axis I diagnosis based on DSM-IV criteria or first-degree relatives with psychiatric diagnoses based upon an interview with the probands. All participants were medically healthy. They were entered into the study after full explanation of the purpose of the study and the study procedures, and after written consent had been obtained as approved by the National Institute of Mental Health Institutional Review Board. Eight remitted MDD patients were naive to psychotropic medications. Twenty-three subjects had a treatment history with psychotropic medications, including selective serotonin reuptake inhibitors (n = 11), serotonin-norepinephrine reuptake inhibitors (n = 5), tricyclic antidepressants (n = 1), benzodiazepines (n = 1), and combinations of the noted medications (n = 5). All patients, irrespective of their treatment during the depressive episodes, met diagnostic criteria for MDD. However, we did not assess the illness burden during these episodes because we did not feel that this information can be sufficiently reliably obtained. No patients had received electroconvulsive therapy.

Magnetic Resonance Imaging

High-resolution images through the temporal lobes were acquired using a GE 3T MRI scanner, a standard head radiofrequency coil, and a magnetization-prepared, rapid gradient echo (MP-RAGE) pulse sequence optimized for gray /white matter contrast echo time [TE] = 2.1 msec, repetition time [TR] = 7.8 msec, prep time = 725 msec, delay time = 1400 msec, flip angle = 6). One hundred twenty four axial slices .6 mm thick were acquired with a 14 cm field of view and in-plane resolution of

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224 x 224 voxels, resampled to 256 x 256 x 124 voxels for reconstruction, resulting in a displayed resolution of .55 x .55 x .6 mm. Three to four 13 minute scans were consecutively acquired, coregistered and summed to increase signal-to-noise. A second MP-RAGE image of the entire brain also was acquired at voxel size = .85 x .85 x 1.2 mm to measure whole brain volume (TE = 4.94 msec, TR = 11.6 msec, prep time = 725 msec, delay time = 1400 msec).

Images were corrected for intensity nonuniformity using the minc tool N3 (McConnell Brain Imaging Centre, Montreal Neurological Institute, Montreal, Canada). For measuring whole brain volume, the nonbrain tissues were removed and the remaining brain image was segmented into gray matter, white matter and cerebrospinal fluid (CSF) images using the FSL tool FAST (FMRIB, Oxford, United Kingdom). Whole brain volume was defined as the sum of gray and white matter compartments.

Hippocampal structures were segmented manually by one rater (SW), blind to diagnosis, in coronal planes using Medx 3.4.1 and anatomical boundaries described by Duvernoy (Duvernoy 1988), after summing adjacent coronal slices (resampled slice thickness = 1.1 mm) to increase signal-to-noise in the plane-of-view. Hippocampus was delimited from amygdala either by the temporal horn of the lateral ventricle or the alveus. The ventral boundary of the hippocampus was defined by the white matter of the parahippocampal gyrus, and the medial boundary by a vertical line placed at the dorsomedial tip of this white matter (to delimit subiculum from parahippocampal cortex). The anterior pole of the hippocampus was defined as the subiculum gray matter lying within the white matter between amygdala and parahippocampal gyrus. In the posterior-most sections, the hippocampal tail was specifically delimited from the pulvinar and caudate tail. The remainder of the head, body and tail were bounded laterally and dorsally by the alveus, lateral ventricle and fimbria. To increase the specificity of the comparisons, the hippocampus was divided into anterior and posterior portions by the anterior-most coronal plane in which the hippocampal head separated from the body.

Intra-rater reliabilities for the volumetric measurements were assessed by computing intraclass correlation coefficients (ICC) between two measures obtained from the same image on separate days from 15 subjects for anterior hippocampus, and 10 subjects for whole hippocampus and whole brain. The repeated measures obtained to assess intra-rater reliability were tightly correlated, with ICC values of $r = .990$ and .952 for left and right anterior hippocampus, respectively, .997 and .993 for the left and right posterior hippocampus, respectively, .981 and .984 for left and right whole hippocampus, respectively, and .999 for whole brain.

Statistical Analysis

One way ANOVA was used to compare the total cerebral volumes and repeated measures. Analysis of covariance (ANCOVA) was used to compare the hippocampal volumes of remitted MDD patients and controls where hemisphere (left vs. right) was the within-subjects factor. Total cerebral volume was the covariate. Hippocampus was evaluated as a whole and in sections; anterior and posterior hippocampal regions were examined separately. Additional ANCOVAs were run including controls and dividing the patient group into those who had a lifetime exposure to psychotropic medications and those naive to medication. Test assumptions were reviewed using Kolmogorov-Smirnov's test for normality and Levene's test for homogeneity of variance. Significance was determined at $p < .05$, two-tailed. Significant main effects and interactions were tested with Bonferroni adjusted simple effects tests.

Partial correlations were used to examine the relations between demographic characteristics and hippocampal volume in the patients where total cerebral volume was controlled.

Results

Healthy controls did not differ from remitted MDD patients in total cerebral volume ($F[1,86] = .25$, $p = .62$). Significant main effects of diagnosis were found for the total ($F[1,84] = 11.40$, $p = .001$) and posterior hippocampal volume ($F[1,84] = 14.80$, $p < .001$), but not for the anterior hippocampus ($F[1,85] = .82$, $p = .37$) (Figure 1).

The total hippocampal volume (main effect of medication exposure: $F[2,83] = 7.26$, $p = .001$) and the posterior hippocampal volume (main effect of medication exposure: $F[2,83] = 7.97$, $p = .001$) were decreased bilaterally in both the drug naïve and the previously medicated subgroups relative to the control group (Figure 1), and these two subgroups did not significantly differ from each other.

Gender, number of episodes of MDD, remission time, and time off medication at the time of the MRI scan did not significantly correlate with hippocampal volume in the patients.

Discussion

The key finding of the present study is that recurrent MDD is associated with reduced volume in the hippocampus. Although the present study does not answer the important question whether smaller hippocampal volumes in the depressed patients may have predated their illness or may be considered a risk factor for a more severe variation of the disease, the data suggest that smaller hippocampal volume is a trait characteristic for MDD.

The smaller hippocampal volume in patients relative to controls was most prominent in the posterior hippocampus. Neuroanatomical and functional imaging studies suggest that the

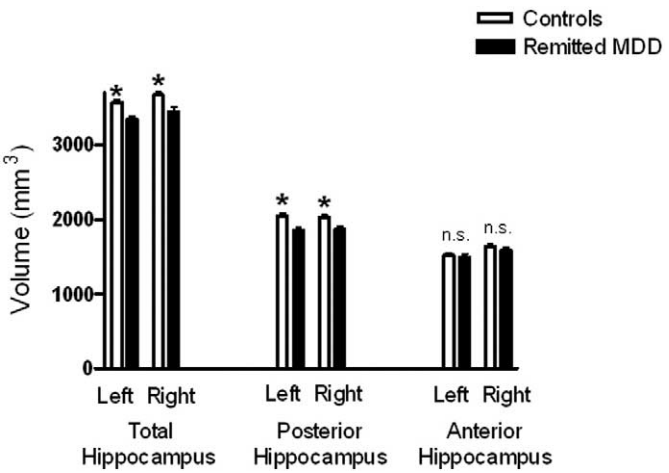

Figure 1. Total, anterior and posterior hippocampal volumes in unmedicated patients with remitted major depressive disorder (MDD) and controls. Data are presented as least squares means and standard error bars. Both, left and right total hippocampal volumes were lower in remitted MDD patients relative to controls ($t = 3.20$, $df = 85$, $p = .001$, and $t = 3.06$, $df = 85$, $p = .002$, respectively). Posterior hippocampal volumes were lower in remitted MDD patients relative to controls on the left and on the right side ($t = 3.95$, $df = 85$, $p < .001$, and $t = 3.24$, $df = 85$, $p = .002$, respectively). No between-group differences were found in the anterior hippocampus.

posterior versus the anterior hippocampus have distinct neuroanatomical projections and functional correlates (Strange and Dolan 1999). Studies in unmedicated symptomatic depressed (Porter et al 2003) as well as remitted (Weiland-Fiedler et al 2004) patients with MDD showed neurocognitive deficits involving spatial learning and memory. These deficits were linked to posterior hippocampus dysfunction in contrast to anterior hippocampus function (Moser et al 1993). Even though the underlying biology remains to be elucidated, cellular changes in the postmortem hippocampus (Stockmeier et al 2004) suggest involvement of serotonergic and neurotrophic systems. Among multiple lines of evidence for serotonergic mechanisms in MDD are studies showing that activation of post-synaptic 5-HT(1A) receptors in the dorsal hippocampus prevents learned helplessness (Joca et al 2003), a process that may be dysfunctional in MDD because of reduced 5-HT(1A) receptor expression that characterizes MDD (Drevets et al 2000). The possibility that serotonergic and neurotrophic hypotheses of MDD are complementary is supported by a recent study suggesting that it is a dysregulation of brain-derived neurotrophic factor homeostasis in the face of a serotonergic perturbation that truly represents a trait vulnerability marker for depression (Neumeister et al, in press).

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